Article No. jaut.1999.0347, available online at http://www.idealibrary.com on IDEAL®

Journal of Autoimmunity (2000) 14, 11–13

Immunologic Hazards Associated with Vaccination of Humans

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Key words: vaccination, immunologic hazards, autoimmunity, autoimmune disease, anti-fertility virus

Universal vaccination remains the most effective measure for preventing the spread of many infectious diseases. Since vaccination is one of the few medical interventions applied to healthy individuals, its safety must be as absolute as human efforts can make it. Questions have been raised recently about the possibility that particular vaccines can trigger or promote autoimmune disease, although controlled, population-based studies have not supported this notion. In collaboration with the World Health Organization, we investigated a subunit vaccine of human chorionic gonadotropin, and found evidence of benign, but not pathologic, autoimmunity. We propose an algorithm for systematic study of possible immunologic hazards of vaccines in animals and human subjects.

No physician who has faced the parents of a child brain-damaged by administration of a vaccine can forget the experience. Many years ago, I attended to a child who had been given a routine injection of pertussis vaccine. He suffered a major neurologic accident and was left hopelessly impaired for the remainder of his life. It was, and will always be, difficult to explain to the parents of such a child why our society mandates immunizations for children. Yet, on a populational basis, it can be objectively shown that universal vaccination remains the most effective measure for preventing many infectious diseases. In the developing countries of the world vaccination is the only practical means at our disposal for controlling the spread of contagious diseases that have arrested the economic growth and condemned the populations of those countries to unremitting poverty and poor health.

Since vaccination is one of the few medical interventions applied to healthy individuals, its safety should, in principle, be absolute, without margin allowed for error. Therefore, the issue of vaccine safety remains paramount in the minds of those involved in developing and promoting vaccines. Vaccines, by their very nature, alter the immune response, creating an abiding concern that adverse consequences may follow. Recently, the question of whether vaccination in general or particular vaccines can trigger or promote autoimmune disease has received added attention in both the scientific and general literature. The introductory article by Shoenfeld and Aron-Maor [1] has reviewed the status of evidence on this issue. Adding the perspective of a laboratory that has for many years been engaged in studies of the immunologic hazards of vaccination may, however, be worthwhile.

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As a World Health Organization Collaborating Center for Autoimmune Diseases, we were asked about 20 years ago to participate in the safety evaluation of anti-fertility vaccines. In addition, we were involved in developing general protocols for evaluation of vaccine safety from immunologic hazards. Many results have been published in WHO sources not widely available to the scientific community and, so, a brief summary of our major findings and conclusions is appropriate.

The goal of our investigations was to evaluate the autoimmune consequences of immunization with an anti-fertility vaccine under trial by WHO [2, 3, 4]. Our studies were carried out initially in baboons and, later, in human volunteers. The vaccine was based on a 36-amino acid C-terminal peptide of the beta chain of human chorionic gonadotropin (hCG). To enhance its antigenicity, the peptide was conjugated to diphtheria toxoid, incorporated into an oil vehicle, squalene-arlacel, and mixed with muramyl dipeptide (MDP), a bacterial product known to serve as an adjuvant. Initially, we had the opportunity of examining serum from two sets of baboons. In the first, a short-term experiment, the animals received (i) saline; (ii) vaccine conjugate, oil and no MDP; (iii) vaccine conjugate, oil and MDP; and (iv) vaccine conjugate, oil and ×10 concentrated MDP as adjuvant. Serum samples were collected before immunization and at 10 and 20 weeks after the start of immunization. The second experiment comprised four groups of baboons, with six animals receiving (i) saline; (ii) oil alone; (iii) diphtheria toxoid, oil and MDP; and (iv) vaccine conjugate, oil and MDP. The animals in this study received a total of six injections at 2-week intervals. Serum samples were collected before the first injection and at bi-weekly intervals until termination of the experiment 18 weeks later. They were studied for a broad array of autoantibodies, primarily by using indirect immunofluorescence on frozen sections of rat and baboon tissue. The immunizations were carried out by Dr Vernon Stevens at Ohio State University,

and the serum samples provided to us in a blinded fashion.

A major early finding of this investigation was that most baboons, as well as most humans, have naturally occurring or preexisting autoantibodies to a large variety of tissues, including smooth muscle and striated muscle. The animals injected with saline alone showed no significant rise in natural autoantibody during the observation period, though occasional random changes in autoantibody levels were found. Nearly all of the other baboons in the study showed rising titers of natural autoantibody. After completion of the immunization protocol, autoantibody levels of some animals declined to preinjection status, although a few samples remained at higher levels. We wondered whether this increase in natural autoantibodies was driven by a particular antigen or resulted from nonspecific stimulation of the immune apparatus by the adjuvant. Our tests, described below, showed that both possible mechanisms occurred.

Following immunization, some sera exhibited reactivity to pituitary tissue. The reactivity appeared to be related to prolactin or growth hormone-secreting cells. An unexpected finding of this investigation was the presence of antibodies to pancreatic islet cells found in the sera of some baboons immunized with the complete vaccine. Double-labeling experiments showed the reactive cells were not the insulin-producing β-cells, but somatostatin-producing δ-cells of the pancreatic islet. The hCG peptide removed the antibody to islet cells, but absorption with somatostatin did not reduce the reaction. The antibody was predominantly IgG and could bind complement. We concluded that the antibodies were directed to a unique antigen of the somatostatin-secreting cells, but not to somatostatin itself.

Serum samples from human volunteers given the hCG vaccine were screened by immunofluorescence for antibodies to a variety of tissues [4]. A number of the natural autoantibodies found in such serum samples were found to rise following immunization. About one third of the samples of human origin contained antibodies to pancreatic islet cells that reacted exclusively with the somatostatin-secreting delta cells.

Our colleagues in the WHO program carried out extensive histological studies of the baboon tissues and found no evidence of inflammation or other immune-mediated damage. In addition, none of the human subjects during the vaccine trial showed any clinical evidence of autoimmune disease.

From these investigations, we concluded that autoantibody development is a frequent event following immunization, but that there is no evidence that this rise in autoantibodies is associated with the development of autoimmune disease. We were of course interested in the possible mechanisms for autoantibody production. Two general mechanisms must be considered. The first is molecular mimicry; that is, the presence in the vaccine of an epitope shared with tissues of the body. The second possibility is that the adjuvant used in the vaccine induces polyclonal stimulation of B cells and increased production of preexisting antibodies. The vaccine employed a 'Freund-like adjuvant', including mineral oil and a mycobacterial product. Our data suggest that both possibilities occurred. Antibodies to striated muscle and to somatostatin-secreted cells were partially absorbed by the hCG peptide and part of the antibody to smooth muscle could be removed by the diphtheria toxoid. Part of the rises in both antibodies, therefore, was probably attributable to antigenic cross-reaction. On the other hand, a more general increase in the preexisting autoantibodies resulted from an adjuvant or bystander effect. In both cases, the autoantibodies produced, however, were benign, since they were not associated with any demonstrable autoimmune damage.

Very few studies similar to ours have been carried out in humans or non-human primates using other vaccines. We would predict that the results might be very much the same; that is, increases in levels of a number of autoantibodies may be due to mimicry or to an adjuvant effect. No evidence for development of an autoimmune disease has yet been found. Since vaccines may be given repeatedly and their effects may continue for a long time, we remain alert for possible autoimmune or other immune-related consequences. To demonstrate such effects requires well-constructed, controlled, epidemiologic studies rather than anecdotal reports.

Fortunately, most careful epidemiologic studies of the association between vaccination and autoimmune disease are beginning to appear in the medical literature. In Finland, the incidence of type 1 autoimmune diabetes is extraordinarily high and complete medical documentation is available on almost the entire population, with very few dropouts. These studies have universally failed to show any connection between any of the standard vaccines, such as measles, mumps and rubella, or any of the newer vaccines, such as *Haemophilus influenzae* type b, and the occurrence of this autoimmune disease [5].

Another precaution is to introduce a systematic study of possible immunologic hazards of vaccines in primates as well as in human subjects undergoing clinical trials. An algorithm for a systematic study of human subjects was proposed by us several years ago [6]. We are not aware that such investigations have regularly been conducted by vaccine manufacturers. Finally, we recognize that even the largest clinical trial might fail to detect individuals with inordinate genetic risk of an adverse autoimmune response. At this time, the evidence available suggests that HLA phenotype is the best predictor of a so-called 'autoimmune diathesis'. We are, however, still at an early stage of unraveling and defining the genetic traits involved in inordinate genetic predisposition to autoimmune disease. Future studies of the human genome may eventually provide us with the data we need to identify in advance humans who are at special risk of developing adverse consequences to immunization.

We also recognize that other risks may accompany vaccination. The recently licensed rotavirus vaccine, for example, seems to have caused several cases of intussusception in children. An additional concern

is that the increasing practice of vaccination may actually produce unwanted levels of organic mercury in children due to the mercurial preservative used in many vaccines. These real concerns for vaccine safety must be distinguished from the purely speculative hazards of autoimmunization.

We must emphasize that the risk-benefit balance is clearly in favor of continuing universal childhood immunization. Vaccines have proven their value in reducing morbidity and mortality of infectious diseases. When popular resistance reduced the use of pertussis vaccine in the UK, the rising incidence of whooping cough greatly exceeded any injury caused by the vaccination itself. Vaccines alone have eliminated one major infectious disease, smallpox, and are well on the way to removing a second threat, polio. It would indeed be tragic if the known benefits of vaccination were imperiled by the unproven risk of autoimmune disease.

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Article No. jaut.1999.0348, available online at http://www.idealibrary.com on IDEAL®

Journal of Autoimmunity (2000) 14, 13–15

Vaccination and Autoimmunity

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Introduction

Vaccines differ from most interventions in medicine in being given to healthy individuals, the beneficial effects being on a statistical rather than an individual basis. This means that safety is an even more paramount concern than with drugs, and the risk benefit equation naturally varies according to the prevalence of the infection of interest within particular communities. All claims regarding adverse effects from vaccines must therefore be taken most seriously.

Fortunately, serious side effects from vaccines are excessively rare and therefore, in the majority of instances, the risk benefit equation is greatly in favour of vaccination. Unfortunately the opponents of vaccination appear to find it difficult to think in statistical terms but it is very important not to commit the mistake of dealing emotionally with their objections. To a large degree, opposition to vaccines comes from industrialised societies where first hand experience of widespread epidemic disease is no longer the norm. Only education, reasoned argument and good statistical and epidemiological research should be used to convince societies of the value of mass education campaigns.

The present discussion of a possible relationship between vaccination and autoimmunity is timely, forming part of a wider debate in which society, including elements of the medical and scientific professions themselves, have claimed a variety of ill-effects of vaccines. Three considerations dictate that adverse effects of vaccines must be taken very seriously. First, vaccines are normally given to healthy individuals in opposition to most other biopharmaceuticals, which are given to the sick. Secondly, most vaccines are given to infants and young children, deemed to be both very precious and very vulnerable. Thirdly, in the industrialized countries, the very success of immunization programs, combined with good personal hygiene, environmental sanitation and improved living conditions, has made epidemic disease seem like something unfamiliar, and perhaps

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something that antibiotics and other medical treatments can cope with. In other words, opponents of immunization can be excused for not understanding the risk–benefit equation of vaccines because of a lack of personal experience. This has to be countered by good education.

Authentic serious adverse effects of vaccines are very rare

Fortunately, serious adverse events following vaccination are very rare. The live attenuated oral poliomyelitis virus vaccine (Sabin vaccine) can rarely revert to neurovirulence. There is one case of paralytic polio for approximately 2.7 million doses of oral polio vaccine, most commonly of Sabin Type 3. This means on average about five such cases in the USA per year. Some have been in vaccines, and some in their contacts. In England and Wales, there were 13 vaccine-associated cases of polio between 1985 and 1991, and the estimated risk of vaccine-associated paralysis was 1.46 per million for the first dose but 0.49 per million for the second and 0 for the third and fourth doses. In all, the nine cases of paralysis arose over 18,400,000 doses of vaccine administered, thus one case per 2,000,000 doses of vaccine, a figure similar to that in the USA. Two of the vaccine-associated cases were in immunodeficient children for whom inactivated poliomyelitis vaccine (Salk) should have been offered.

In 1994, 8,000,000 children aged 5–16 were immunised with measles–rubella vaccine in the UK. Great effort was taken to ensure that any adverse reaction was reported. Most reactions were minor and self-limiting, but 530 children had a serious reaction (0.007%) none of which had a fatal outcome. There were 91 reports of serious neurological reactions including 11 of encephalitis. A definite diagnosis was made in only six of these. The number of reports of encephalitis is less than the background frequency estimated from epidemiological studies. There was one child with sub-acute sclerosing pan-encephalitis. This developed 1 month after immunization and as the usual incubation period after an attack of a wild measles infection is much longer, it seems unlikely that the vaccine was responsible. Given the rarity of the neurological complications, a cause and effect relationship is difficult to sustain.

Another interesting complication of measles immunization is thromocytopaenic purpura, variously reported at 1/100,000–1/500,000 vaccinations. In the UK study, the reported incidence was much lower, namely seven cases in all or 1 in 1,100,000. This particular complication was usually self-limited. The incidence of a similar complication in natural measles has been variously estimated at 0.1–1%. While a plausible causal relationship can be argued in this case, the complete recovery in at least 90% of cases and the absence of mortality shows that this rare complication does not modify the risk-benefit equation significantly.

Vigilance must be especially intense during vaccination campaigns

It is especially important that care be taken with the reporting and analysis of adverse effects during government-sponsored intensive immunization campaigns. For example, the small number of cases of Guillain–Barré syndrome associated with President Ford's influenza vaccination campaign of 1976 was a statistically greater number than might reasonably have been expected. These cases were in part responsible for the cessation of the campaign, although the failure of 'swine flu' to spread from the single patient at Fort Dix probably represented the major reason.

Making vaccination safer still

Where possible, genuine risks associated with vaccines should be lowered still further by improvement to the vaccine. Thus in the USA, a rich country which can afford the more expensive vaccination option, it is now recommended that infants be immunized against poliomyelitis either by two doses of injectable poliomyelitis vaccine followed by two oral doses, or by four doses of the injectable vaccine. The most controversial vaccine from the viewpoint of side effects has been diphtheria–pertussis–tetanus containing whole killed pertussis bacteria. Reactions such as fever, irritability, local redness, swelling, pain, anorexia and drowsiness are quite common, though of short duration, and it is believed that this is due to the whole killed pertussis bacteria within the vaccine. The question of serious acute neurologic illness, e.g. encephalopathy, has caused the most concern. Various studies put the incidence of this somewhere between 0 and 1 in 200,000. It is now possible to gain equivalent protection against pertussis with an acellular pertussis vaccine consisting of 3–5 molecular components in pure form. The acellular pertussis vaccine has certainly caused less acute reactogenicity, as measured by the superficial parameters described above. Given the exceedingly rare nature of the serious neurological alleged complications, it will take a great deal of experience and study over a number of years to determine whether these are less frequent with the purer vaccine.

Not all parents of unimmunized children are opponents of vaccination

Overall, some 80% of the world's children are receiving the six common childhood vaccines during infancy. The incidence from country to country varies from a low of perhaps 40% to a high of about 95%. In the industrialized countries, a plateau at around 80% has been reached in many cases. Where the subject has been studied, it is clear that only a minority of the parents of such children actually oppose vaccination on intellectual grounds. Indeed, it has been estimated

that only about 2% of parents fall in this group, the rest are difficult to reach, apathetic or otherwise lacking in motivation. In many countries, the children of such parents are protected by herd immunity, and an interesting change in trends occurs when there is a brisk little epidemic caused by the immunization rate falling below a certain threshold (typically around 75%). For example in the case of whooping cough, a relatively small amount of publicity showing hospitalised, very sick cases will send the mothers and babies scurrying to the vaccination centre in quite a hurry! In this regard, we have not been worrying enough about booster doses following basic infant immunization. During the brisk diphtheria epidemic in the countries of the former USSR in 1995 and 1996, a significant proportion of the cases were in adults. Whereas many adults have tetanus boosters, e.g. when they injure themselves, few countries have active plans for regular diphtheria boosters.

Autoimmunity and Immunization

Drs Shoenfeld and Aron-Maor have done an excellent job in summarizing the current literature on the possibilities of vaccines acting as a trigger for autoimmune phenomena. The story of hepatitis B vaccine and multiple sclerosis is most interesting. A very modest but nevertheless clear-cut and possibly statistically significant increase in demyelinating disease in adults immunized with hepatitis B vaccine has been noted in France, a country in which a very active whole-of-population campaign has been introduced. In the USA, on the other hand, no such association has been noted. United States authorities have concluded that perhaps their follow-up procedures are suboptimal. Demyelinating phenomena appear not to have been noted in infants or young children. As most countries now have hepatitis B immunization as part of the national plan in infancy, it well may be that this problem (if it is one) is self-solving. These authors conclude that the issue of the risk of vaccination remains a philosophical one, as the risks remain somewhat conjectural but the benefits represent a public health triumph of major dimensions. To this the present author would only add that the risk-benefit equation is tilted vastly in favour of immunization in the developing countries, where three-quarters of the deaths which occur in the under-14 age-group are due to communicable diseases. Of course, the problem at issue would disappear, disease by disease, if eradication attempts were to be successful. We have eradicated smallpox, are well on the way to eradicating poliomyelitis, and can envisage the possible eradication of measles were sufficient resources devoted to the problem. Many other disease could potentially be eradicated. On balance, this is the shining goal for 21st century preventive medicine.

Article No. jaut.1999.0349, available online at http://www.idealibrary.com on IDEAL® Journal of Autoimmunity (2000) 14, 15–22

Stimulation of the Developing Immune System Can Prevent Autoimmunity

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Both genetic and environmental factors contribute to the development of autoimmunity. Animals and humans exposed to natural infections have a reduced rate of autoimmune diseases. There is increasing evidence that immune stimulation prevents autoimmune diseases. Our hypothesis is that the process of the development of pathogenic cells involved in autoimmunity can be modulated by early stimulation of the immune system in autoimmunity prone individuals This allows for the upregulation of cytokines and growth factors that influence the generation of regulatory cells involved in autoimmunity. As we live in a 'cleaner environment' the decreasing chances of natural infection in the general population may contribute to the induction of autoimmunity because the developing immune system is not exposed to stimulation that may be necessary to generate regulatory cells involved in the modulation and prevention of autoimmunity. Immunization with certain vaccines may provide an alternative approach to stimulate the immune system to modulate or prevent the generation of pathogenic cells involved in autoimmunity by induction of regulatory cells.

Key words: Immunostimulation, immunoregulation, regulatory T cells, vaccination, infection, autoimmunity

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Abstract Volume 43 Issue 10 (2000) pp 1229-1234

Infections and risk of Type I (insulin-dependent) diabetes mellitus in Lithuanian children

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Received: 1 March 2000/and in revised form: 13 June 2000

Abstract

Aims/hypothesis. The role of infections in the aetiology of Type I diabetes is controversial. Certain enteroviral infections might be involved in triggering the beta-cell destruction but insufficient exposure to early infections might increase the risk. We studied how the number of infections experienced during several periods from birth to onset influence diabetes risk.

Methods. The study group came from the five largest Lithuanian cities: 124 patients, selected from the 0-14 years-of-age childhood diabetes register and 372 population-based control subjects matched with them for age group and sex. Information about infections and duration of breastfeeding was collected from health care booklets, other data from a mailed questionnaire, returned by 94.4 % of patients and 72.6 % of control subjects.

Results. One or more infections experienced during the first half year of life tended to reduce diabetes risk. Crude odds ratios (95 % confidence intervals) in the 0-14, 0-4 and 5-14 years-of-age groups were 0.66 (0.42-1.04), 1.06 (0.48-2.36) and 0.52 (0.30-0.90) respectively. Adjustment for the duration of breastfeeding, number of people in the household, duration of mother's education and birth order of the index child made little difference. Odds ratios (95 % confidence intervals) in the 0-14, 0-4 and 5-14 years-of-age groups were 0.60 (0.37-0.98), 0.94 (0.40-2.20) and 0.47 (0.26-0.87), respectively. The number of infections recorded during the last pre-onset year or from birth to onset did not influence diabetes risk.

Conclusion/interpretation. Exposure to infections early in life could decrease diabetes risk, particularly for children diagnosed after the age of 4 years. [Diabetologia (2000) 43: 1229-1234]

that only about 2% of parents fall in this group, the rest are difficult to reach, apathetic or otherwise lacking in motivation. In many countries, the children of such parents are protected by herd immunity, and an interesting change in trends occurs when there is a brisk little epidemic caused by the immunization rate falling below a certain threshold (typically around 75%). For example in the case of whooping cough, a relatively small amount of publicity showing hospitalised, very sick cases will send the mothers and babies scurrying to the vaccination centre in quite a hurry! In this regard, we have not been worrying enough about booster doses following basic infant immunization. During the brisk diphtheria epidemic in the countries of the former USSR in 1995 and 1996, a significant proportion of the cases were in adults. Whereas many adults have tetanus boosters, e.g. when they injure themselves, few countries have active plans for regular diphtheria boosters.

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LDS HOSPITAL STUDY FINDS POSSIBLE LINK BETWEEN TIMING OF COMMON PEDIATRIC VACCINES AND DEVELOPMENT OF TYPE 1 DIABETES

SALT LAKE CITY – Up to 25 percent of cases of insulin dependent diabetes mellitus that occur before age 15 may possibly be prevented by immunizing children with common pediatric vaccines at birth, rather than waiting until up to eight weeks of life, according to a new epidemiological study by researchers at LDS Hospital in Salt Lake City and Classen Immunotherapies in Baltimore, Maryland.

Results of the analysis, which are published in today's issue of the journal, *Infectious Diseases in Clinical Practices*, suggest that the timing of common pediatric immunizations may alter the development of insulin-dependent diabetes in humans. Investigators say vaccines given at birth may possibly prevent children from being colonized with diabetes-inducing viruses from their mother.

The lead author of the paper is David C. Classen, MD, a researcher in the division of infectious disease at LDS Hospital and faculty member of the University of Utah School of Medicine. Co-author is J. Barthelow Classen, MD, MBA, from Classen Immunotherapies.

Utilizing epidemiological and statistical models developed at LDS Hospital, the researchers compiled and compared data from European countries that show immunization at birth with the BCG vaccine, a common vaccine used to prevent tuberculosis, may be associated with the equivalent of a 33 percent reduction of insulin-dependent diabetes in most European countries by age 15.

By contrast, the analysis showed immunization with the BCG vaccine starting at school-age may be associated with a substantial increased risk of insulin-dependent diabetes. Data included in the paper also link rises in the incidence of the disease, also know as Type 1 diabetes, to the administration of the hepatitis B and hemophilus B vaccine in children who were vaccinated after they were two months old.

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The incidence of the Type 1 diabetes was correlated with immunization schedules in all Western European nations (except Germany) from 1986-1990 because of the extensive diabetes registries maintained by each country. Also, immunization schedules in those nations vary, giving investigators an opportunity to compare data.

The epidemiological data supports findings from previous animal studies conducted by Classen Immunotherapies (Autoimmunity, 1996, 24:137-145), that found that immunization of rodents at birth with common pediatric vaccines was associated with a decreased risk of Type 1 diabetes while administration of the whole cell pertussis vaccine at eight weeks of life was associated with an increased risk of the disease.

How might this occur? Dr. David Classen suggests that immunization with a wide variety of vaccines may alter the risk of Type 1 diabetes by the release of interferon and other immune mediators in a newborn's system.

"Interferon released at birth following immunization may prevent children from being colonized with diabetes-inducing viruses from their mother," says LDS Hospital's Dr. Classen, a board-certified specialist in internal medicine and infectious disease. "By contrast, after children are eight weeks or older they may have sub-clinical inflammation of insulin secreting cells that may be enhanced by immunization leading to insulin dependent diabetes.

"Based on our epidemiological data and previous animal studies, there appears to be a very tight window in which conditions are ideal to administer the first dose of common vaccinations," he says. "The next step is to verify this hypothesis with a large clinical trial involving humans, either in the United States or abroad.

"If the findings bear out, the benefit in the reduction of human suffering and associated health care costs from Type 1 diabetes may be tremendous," says Dr. David Classen. It's estimated that more than $30 billion is spent annually in the U.S. alone to treat people with insulin-dependent diabetes.

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